EFFECT OF PRESSURE ON SOLID-SOLID INTERACTIONS

by SAMUEL LAURENCE FORUSZ

(Under the supervision of Professor Dale E. Wurster)

Recently, increasing attention has been focused on both chemical reactions and physical interactions in the solid state. The nature of these changes are of particular importance in pharmacy in the formulation of solid dosage forms because they can affect not only the physiological availability of a drug, but also its stability. Although most solid dosage forms involve the use of compressional forces at some stage of their production, the knowledge pertaining to the interactions that occur between ingredients during, and just after, compression is limited. This is due, most probably, to the difficulty involved in the analysis of the solid state.

In the search for a suitable system for investigation, solid complexes were prepared from solution and their stoichiometries were determined. The study of the complex containing 1 mole p-aminobenzoic acid:1 mole caffeine showed that it also contained 3 moles of water and was not anhydrous, as previously reported. Another study on the interaction of succinamic acid with p-aminobenzoic acid and m-aminobenzoic acid in solution showed that these were not physical interactions but chemical reactions as a new chemical bond was formed in each case with the elimination of ammonia.
The effect of pressure on solid-solid interactions was investigated utilizing various molecular mixtures of p-aminobenzoic acid, oxalic acid and water. In addition, a known complex containing one mole each of these three compounds was used as a model or reference, after its nature and properties had been determined. The mixtures and the complex were compressed in a specially designed punch and die holder by means of a hydraulic laboratory press.

In order to study the influence of pressure, it was necessary that a sensitive and accurate method of analysis be employed. Methods were developed employing differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) for quantitatively monitoring the changes that occurred on compression. This application of these thermal methods to the study of the kinetics of complex formation is a new one, first utilized in this study.

All quantitative work was carried out using the above TGA and DSC methods, although some qualitative information was obtained from nmr, ir, and X-ray studies.

Comparison of the thermograms obtained after compression of mixtures, at constant time and pressure, containing different molar quantities of water, showed that increased water content brought about increased interaction under pressure. It was observed that on compression of a 1:1:2 aged molecular mixture of PABA, oxalic acid and water, that it was converted to the 1:1:1 known complex with water being "squeezed" from the mixture. Mixtures containing less than
two moles of water did not undergo any change. The effect of various pressures on the kinetics of complex formation was demonstrated by compressing the 1:1:2 mixture at constant time. The results indicated that the interaction followed apparent first-order kinetics and that the rate of complex formation increased as the pressure increased. Compression of 1:1:2 mixture at constant pressure for different times indicated that the kinetics of complexation were again apparent first-order and that the rate of complex formation increased as the time of compression was increased. A linear relationship was found to exist between the rate constants and the compressional force, whereas, a nonlinear relationship existed between the rate constants and the time of compression.

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DATE
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TO MY WIFE, JUDY,

WITH LOVE AND AFFECTION
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INTRODUCTION

It was in 1843 that an Englishman, William Brockedon, applied for a patent on the first machine "for shaping pills, lozenges and black lead in a pressure die" (1,2). Since that time, the great advances in engineering and pharmaceutical technology have brought about the evolution of the tablet machine from a manually operated single punch instrument into a highly efficient multipunch automated machine capable of producing thousands of tablets per minute. These advances, together with accuracy of dose, ease of administration and portability, have made the tablet the dosage form of choice, especially when drugs have to be given on a continuing basis.

The kinetics of chemical degradation of the active compounds in tablets under such influences as temperature and moisture have been investigated thoroughly by many workers. Some of the physical aspects of tableting, such as compressional force, hardness, disintegration time, die-wall pressures, etc., and their relationships to one another have also been explored. However, much work remains to be done to elucidate not only the solid state changes that occur in tablets, but also the mechanism whereby these changes are brought about. As an example of the many problems encountered in designing solid dosage forms like tablets, it is not uncommon for a particular formula to produce unexpectedly high (3,13) or
low (4) blood levels, either in a particular patient at different times or in most patients at all times (5), than was indicated in clinical trials with the pure drug. Some tetracycline formulations, specifically have given rise to this type of problem. When calcium diphosphate was used as a filler in tablets of this antibiotic (6,7), complex formation occurred between the calcium and the antibiotic which resulted in lower blood levels than expected (3A). When the problem was recognized, it was easily overcome by changing the filler. Also, it was found that if patients took antacids containing calcium, aluminum, magnesium (8), or drank milk (9) when taking this particular antibiotic, a similar phenomenon resulted (4), due to the strong interaction between tetracycline and the metal ions.

Obviously, then, the poor performance of both solid and liquid dosage forms can be associated not only with chemical degradation of the therapeutic agent, but also with interactions between individual components of the formula or body fluids. While most interactions between ingredients occur in solutions, it is possible that certain physical influences can aid in initiating some of these interactions even in the solid state.

Reports of both physical and chemical influences are now appearing somewhat more often in the literature; however, knowledge pertaining to interactions that occur between the tablet ingredients during, and just after, the compressional process has advanced very little since
Brockedon's day. The fact that such interactions do occur even in the solid state (10-12,14,44) is of great importance in the formulation of solid dosage forms, as these interactions, as previously indicated, can affect not only the availability of the drug for absorption, but the stability as well. Thus, in an attempt to gain some insight into certain of these solid state interactions, the effect of pressure under various conditions was studied on molecular mixtures of p-aminobenzoic acid, oxalic acid and water. The effect of pressure on a known 1:1:1 complex of these three compounds was also studied. The pressure effects were followed by means of differential scanning calorimetry and thermogravimetric analysis.
PAST WORK

One reason for the relatively small amount of work that has been done in the field of solid state interactions is the difficulty in analyzing the solid phase. The forces involved in interactions or reactions in the solid state are, of course, either physical or chemical in nature, although sometimes both can be involved (15). Chemical reactions often involve the formation of new covalent bonds, usually with the elimination of one or more atoms from the reacting molecules. Physical interactions can involve either the much weaker forces, such as hydrogen bonding and van der Waals' (15), or charge transfer and electrostatic forces.

Up until 1962 when Rastogi, Bassi and Chadha (14) described their technique for studying the kinetics of reaction between naphthalene and picric acid in the solid state, most of the work in this area had been limited to reactions which could be followed by X-ray crystallography or by measuring the amount of gas evolved in suitable reactions (17). Rastogi, Bassi and Chadha and Rastogi and Singh (18,19) carried out a series of reactions in the solid state involving picric acid and naphthalene, naphthols and other substituted naphthalenes, both below and above their eutectic points. The start of the reaction was indicated by a color change, at the boundary between the picric acid and
the naphthalene, which migrated along the reaction tube as the reaction proceeded. Naphthalene and its derivatives penetrated into the picric acid; the rate of reaction being determined by the lateral diffusion of naphthalene in the product layer. Rastogi and Singh concluded that the mechanism was one of lateral surface diffusion, rather than one of vapor phase diffusion, since experiments showed that diffusion did not occur through the vapor phase and that the activation energy for the reaction was less than the heat of sublimation. The rate of the reaction was found to be dependent on temperature and particle size. The reaction resulted in the formation of 1:1 complexes. Diffuse reflectance spectra (DRS) and dipole studies indicated that only weak interactions were involved (dipole-dipole type), and infrared studies showed the absence of hydrogen bonding. They derived the following equations (14):

\[ \xi^2 = 2k_1 \text{te}^{-P \xi} \quad \text{(Eq. 1)} \]

which they later modified, to show the dependence on surface area and diffusion, to (18)

\[ \xi^2 = 2AD \text{te}^{-P \xi} \quad \text{(Eq. 2)} \]

where \( k_1 = AD \) and \( \xi \) denotes thickness of product layer at any time \( t \), \( A \) denotes surface area of particles, \( D \) denotes
the diffusion coefficient and $P$ a proportionality constant. Since the diffusion coefficient was temperature dependent they showed that (18)

$$k_i = 4n_\gamma r^2 D_0 e^{-E/RT} \quad \text{(Eq. 3)}$$

where $D_0$ denotes a constant, $E$ denotes the activation energy, $T$ denotes the temperature and $4n_\gamma r^2$ the area of $n$ particles. The preceding work by Rastogi, et al. was thus the first major attempt to quantify a solid state reaction.

In 1944, Milorat (20) reported a colored reaction between L-ascorbic acid and nicotinamide. In 1945 this reaction product was isolated as a yellow crystalline powder by Bailey, Bright and Jasper (21) who also described the preparation of a similar compound of nicotinic acid and L-ascorbic acid. Wenner (15), in 1949, described the same compounds and showed that the reaction also occurred with d-isoascorbic acid and nicotinamide, but not with nicotinic acid. Wenner (22) also showed that the time of formation varied with temperature and solvent used, indicating that the reaction was not simple salt formation, but also involved a secondary valence linkage—possibly that of a hydrogen bond. The reaction also occurs in the dry solid state (L-ascorbic acid and nicotinamide) and is covered by a patent taken out by Fox and Opferman (23). The structure for the nicotinic acid complex was suggested
by Wenner and confirmed by Najer and Guépet (24) who also worked out the structure for nicotinamide-1-ascorbic acid complex. Bailey, et al. indicated that dissociation of the salt occurred in solution (21).

![Structural formula of Nicotinic acid-1-ascorbate complex and Nicotinamide-1-ascorbate complex](attachment:image.png)

Solid state reactions resulting in the formation of new covalent bonds have been carried out by Gluzman (25-34) who has done much work on the acylation of solid amines with solid acylating agents. Initially the compounds were ground together in a mortar and it was found that they converted into solid products without apparent formation of intermediate liquid products (eutectics). Care was taken to carry out these reactions at temperatures below the eutectic points. It was shown by Gluzman and Plotkina (26) and Gluzman and Milner (33) that the yield of the reaction
product increased with an increase in temperature (often spontaneous) accompanied by an increase in the diffusion rate. Gluzman and Milner (29,30) found that in the acylation of solid amines with solid anhydrides little or no reaction occurred via the gaseous phase, but that the bulk of the reaction was due to contact between the two solid reactants and that lateral diffusion played a part in propagating the reaction. Also, they found that the thickness of the product layer was the limiting factor, as did Rastogi (18) later on. Gluzman and Arlozorov (31) determined the effect of increased pressure on the reaction of equi-molecular mixtures of acid anhydrides and amines. The pressure used was 1550 Kg/sq.in. and the temperature of the die was maintained just below the eutectic point. Lower yields resulted after compression which they ascribed to higher melting points of the eutectics.

Gluzman and Milner investigated acylation under isothermal conditions (34) and by heating the mixtures at a constant rate of 0.5°C per minute (33) with the result that the yields were almost always in excess of 95%. The type of reaction was

\[
\begin{align*}
\text{CH}_2\text{CO} & \quad \text{COOH} \\
\text{CH}_2\text{CO} & \quad \text{NH}_2 \\
\text{HN-} & \quad \text{COOH} \\
\text{C-CH}_2\text{CH}_2- & \\
\text{succinic anhydride} & \quad p\text{-Aminobenzoic acid} & \quad \text{N-(4-Carboxyphenyl)-succinamic acid}
\end{align*}
\]
Nowhere does it appear that any attempt was made by Gluzman, et al., to exclude moisture. It is quite possible that moisture could play a part in propagating the above reactions.

It was not until Lach and Bornstein (35) published their first paper on solid-solid interactions that any real attempt had been made to investigate solid interactions in pharmacy, other than degradation reactions in solid dosage forms. Using diffuse reflectance spectroscopy (DRS), at about the same time as Rastogi (18), they investigated the optical properties of adsorbed molecules of oxytetracycline and anthracene, among other compounds, onto magnesium carbonate. This was the first attempt to apply DRS to pharmaceutical complexes and to recognize interactions in the solid state. Rastogi and Singh (18) used DRS successfully in determining alpha- and beta-naphthol-picrates later. The general method of bringing about adsorption of the active compound onto the adsorbent was to disperse the adsorbent and adsorbate in a liquid medium (either aqueous or nonaqueous) and then allow the mixture to equilibrate for 24 hours. After equilibration, the powder was filtered and dried and the DRS was measured. Lach and Bornstein (35-37) concluded that these were donor-acceptor solid-solid interactions probably of the charge transfer type described by Mulliken (41) involving a Lewis acid and a Lewis base. In their subsequent two
papers \((36,37)\) they applied the above procedure to prednisolone, hydrochlorothiazide and oxytetracycline with various adjuvants. Bornstein and Lach, together with Walsh and Munden \((38)\), also studied dye-adjuvant chemisorption and showed that a metallic or polyfunctional adsorbent molecule was necessary for these interactions to take place. Together with Munden \((39)\) they investigated iron-adjuvant interactions and showed that iron is adsorbed onto various adjuvants such as magnesium oxide or magnesium carbonate.

One important study which Lach and Bornstein did not pursue after their first paper \((35)\) was that of interaction by compression. They prepared mixtures of adsorbent and adsorbate, compressed them at various pressures, then measured the DRS of the tablet as a whole, the powdered tablet and the original mixture. The DRS showed differences indicating that an interaction had taken place in the oxytetracycline hydrochloride-magnesium trisilicate mixture and that increased pressure brought about increased interaction. When the mixture alone was exposed to water and dried, but not compressed, DRS indicated interaction had taken place \((36)\).

Guillory, Soon and Lach \((40)\) have recently made a critical evaluation of thermal methods in detecting possible interactions between pharmaceuticals in the solid state. Differential thermal analysis \((DTA)\) was compared with the cooling curve method and the melt method to obtain phase
diagrams for binary systems. DTA was shown to have advantages over the other two methods. A series of systems was found in which interactions (complexation) could be detected.

French and Morrison (11) identified complexes of phenobarbital with quinine, quinidine and hydroquinone in a number of pharmaceutical dosage forms by means of infrared spectroscopy using KBr disks. Papariello, Lettermann and Huettemann (43) applied X-ray diffraction techniques to try to analyze tablets. They found that of the tablets tested, only in glutethimide tablets, where the percentage of active component was high, was analysis of the intact tablet possible. They concluded that at least 50% of the formulation must be drug before X-ray diffraction can be contemplated.

Tablets containing aspirin have been the source of several recent papers on chemical interactions in the solid state. Troup and Mitchner (12) reported that phenylephrine underwent acylation in compressed tablets containing aspirin. Under accelerated conditions the mono-, di-, and tri-acylated products were identified. Koshy, Troup, Duvall, Conwell and Shankle (42) showed the acylation of acetaminophen in tablet formulations containing aspirin resulted in the formation of diacetyl-p-aminophenol (DAPAP) or p-acetoxyacetanilide. DAPAP was detected by thin layer chromatography. A
procedure to determine the amount of DAPAP using a partition column and gas liquid chromatography was developed. It was interesting to note that the presence of magnesium stearate accelerated the reaction. This method is quantitative as the reaction product can be assayed, but it is not practical for following the rate of the reaction in the solid state.

Jacobs, et al. (44) reported the reaction between aspirin and codeine resulting in the formation of acetyl codeine. They showed that the reaction was dependent on water in the lower regions, but at higher moisture levels an increase in rate showed less of a dependency. It was suggested by them that the reverse reaction became more evident at higher moisture concentrations (2% maximum).

So far almost all the methods mentioned for studying solid interactions have been qualitative. With the exception of Rastogi’s work (14), those methods which were quantitative were useless in following the reaction kinetically and only useful in determining the amount of reaction product after a long period of time.

Much work on the fundamental problems of tabletting has been done since it was started by Higuchi, et al. (46) in 1952. With the exception of the few relatively recent papers (10-12,31,42-44), very little has been reported on the action of pressure in bringing about interactions between organic compounds in the solid state. Sood and Stager (45) have applied high pressure to inorganic
hydrates and have shown that either dehydration to lower hydrates or irreversible phase transformations occurred.

In the above survey only cases where association of molecules have occurred, either physically or chemically, have been considered. Degradations of active drugs have not been a prime consideration because, as noted previously, they have been investigated very thoroughly by many workers in the past.

**Thermal Methods of Analysis**

Le Chatelier (47) first described the technique of differential thermal analysis in 1887. Since that time this type of analysis has been applied almost exclusively to clays, soils and minerals. In recent years, DTA and the related technique of differential scanning calorimetry (DSC) have been extended to many different fields, including pharmacy, for the detection and estimation of impurities (48) and for the identification of polymorphic forms and solvates (48). DTA, which gives higher temperature accuracy, and DSC, which gives the most accurate quantitative data for heats of transition, have been used to study eutectics (40), produce phase diagrams in binary systems (40,49,51), to follow chemical reactions and determine melting points of derivatives of such reactions (50). The measurement of the DSC peak area has been determined by many different constructions (52). The Berg
methodology (53), with slight modifications, was used in determining the peak areas in this study.

The first thermobalance was developed by Honda in 1915, but it was not until 1947 when Duval applied it to inorganic gravimetric analysis that interest in thermogravimetric analysis (TGA) was stimulated (54).

Kinetic studies have been carried out using all of the above techniques and have been confined to the reaction kinetics of homogeneous reactions (55,56,61) (melting, boiling, phase transitions, dehydration and decomposition). From the slopes of the DTA, DSC (57) and TGA (58,60) curves the activation energies, the rate constants and order of reaction have been determined. Also, from the shift in DSC or DTA peak temperature at different heating rates (59), it is possible to determine both the activation energy and the rate constant.
PLAN OF STUDY

As previously shown, interactions do occur in the solid state. If they occur at ambient conditions, then it would be expected that they should also occur under compression: the pressure aiding the interaction due to thermal influence and by bringing the molecules into closer proximity. In an attempt to gain some insight into the effect of pressure on solid-solid interactions, the following areas of study were considered. It was thus assumed that the compressional force could aid in bringing about association between molecules in a mixture and that the amount of interaction would be proportional to the pressure exerted. Further, it was anticipated that the time of compression (residual time in die) and the moisture content of the mixture could also affect the degree of interaction. In order to study these possible influences it was necessary that a suitable system be designed and a sensitive and accurate method of analysis be employed.

Selection of a System

Various solid complexes were prepared from solution and their stoichiometries determined. It was decided to use the complex containing one mole each of p-aminobenzoic acid, oxalic acid and water as the model or reference. Various molecular mixtures of these components were prepared
containing from one to three moles of water and subjected to pressure to try to effect the conversion of the mixtures to the complex.

**Selection of Analytical Method**

There are very few readily available methods of analysis for solids in the solid state and still fewer which are suitable for a system consisting of more than one component. This difficulty in analysis is probably the reason why so little work has been done in this area. The analytical method of choice had to satisfy two conditions: firstly, that it would be able to indicate when an interaction had occurred, and secondly, that it would enable the extent of the interaction to be estimated in the solid state. The requirement that the assay be carried out in the solid state was necessary because interactions are more likely to occur in solution than in the solid state, and solution methods of analysis might indicate a positive interaction when in fact none had occurred in the solid state. Further, the stoichiometry of the solid complex might be changed or the complex might be broken in solution. For these reasons, solution methods of analysis were rejected.

By the elimination of unsuitable solid state methods of analysis for the particular system under study, including infrared and X-ray diffraction patterns, thermogravimetric
analysis and differential scanning calorimetry were chosen as the best methods to meet the above requirements.

Differential Scanning Calorimetry (DSC) and Thermogravimetric Analysis (TGA)

It is known that different compounds and different crystalline forms of a compound have different thermal characteristics. It would follow then, that if complexation had taken place under pressure there would be a difference in the thermal properties of the compressed and uncompressed mixtures. This happened to be the case. DSC and TGA have the advantage, over the spectrophotometric methods tried, of being simpler to interpret and of giving a direct indication of complex formation.

Differential scanning calorimetry is a quantitative method of measuring the enthalpy changes that occur when a known weight of a compound is heated at a constant rate in a furnace. The area underneath the curve of the DSC thermogram, where it departs from the baseline, is directly proportional to the enthalpy difference between sample and reference. The enthalpy change is calculated from the peak area by substitution into the following equation (65) when the Dupont 900 x-y plotter is used:

$$\Delta H(\text{mcal/mg}) = \frac{E.A.\Delta Ts.Ts}{M.a} \quad (\text{Eq. 1})$$
where

\[ E = \text{calibration coefficient mcal/°C-min} \]
\[ A = \text{peak area in square inches} \]
\[ \Delta T_s = \text{y-axis sensitivity setting °C/inch} \]
\[ T_s = \text{x-axis sensitivity setting °C/inch} \]
\[ M = \text{sample mass mg} \]
\[ a = \text{heating rate °C/min} \]

The calibration coefficient \( E \) was found using indium, with \( \Delta H \) fusion equal to 6.79 cal/gm, as it gives a suitable \( E \) value for the temperature range 100°C–165°C.

Various geometric methods have been used to construct the best baseline for the DSC peak when baseline shifts occur. The methods used by Berg (53) are applicable where baseline shifts are due to specific heat or thermal conductivity changes in the sample. Specific heat changes are generally associated with dehydration or decomposition reactions whereas new phase formation, or transition into another state of aggregation, brings about thermal conductivity changes.

Thermogravimetric analysis is a quantitative method of measuring the change in weight of a compound when it is heated at a constant rate on the pan of a thermobalance enclosed in a furnace. The weight loss or gain can be measured directly from the TGA curve.
Application of DSC and TGA to the Study of the Kinetics of Complex Formation Between PABA, Oxalic Acid and Water

Both DSC and TGA curves have been treated to yield reaction kinetics of the type

\[ \text{solid A } \rightarrow \text{solid B + gas} \quad (\text{Eq. 2}) \]

This type of kinetics has been studied thoroughly in the past for dissociation and dehydration reactions \((54-56,66)\). The object in this study was not to follow the reaction kinetics of the mixtures by DSC and TGA, but to follow the changes that occur with time in the compressed mixtures. The application of DSC and TGA to the study of the kinetic rate of complex formation (interaction) in the solid state, under various conditions of pressure, moisture content and compression time, is a new one, first utilized in this study.

To date, no kinetics have been developed specifically for the treatment of solid-solid interactions, although kinetic treatments for drug degradations in both solid and liquid dosage forms are quite common in the literature. Zero order \((70,75,76)\) and first order \((67,69-73,75,78)\) kinetics are the usual types encountered in degradations in pharmaceutical dosage forms, although, sometimes second order kinetics are found \((77)\). Garrett, et al. have shown that fumagillin followed first order kinetics \((67)\) when it
degraded photolytically, and second order kinetics (68)
when it underwent thermal degradation, both in the presence
of air. Carstensen, et al. (69-73) have shown that
vitamin A palmitate and acetate, and thiamine hydrochloride
(73) degrade by pseudo first order kinetics in the presence
of moisture. If the rate of interaction of the components
of the molecular mixture is dependent upon the amount of
water present, and if the interaction reaches an apparent
equilibrium then the kinetics may be similar to those of
the formation of the degradation product of vitamin E
succinate (72), or of the decomposition of vitamin A as
each approaches an apparent equilibrium (72).

The system described by Carstensen (72) is one where
the forward and backward reactions are both first order:

\[ \begin{align*}
A & \xrightarrow{k_+} B \\
& \leftarrow \xrightarrow{k_-}
\end{align*} \quad \text{(Eq. 3)}
\]

where \( k_+ \) and \( k_- \) are the rate constants for the forward and
backward reactions. The kinetic equations will be derived
for this system (74). The assumptions are made that an
equilibrium value is approached or indicated and that at
zero time no B is present in the system. Let \( X_e \) be the
equilibrium concentration of B, \( X \) the concentration of B
at any time \( t \) and \( A_0 \) the initial concentration of A.
(1-\( X \)), then, denotes the concentration of molecule A at any
time \( t \). The rate of formation of B is given by:
\[
\frac{dB}{dt} = \frac{dX}{dt} = k_+(A_o - X) - k_-X
\]  \hspace{1cm} (Eq. 4)

At equilibrium the rate of the reaction is zero, and \( X = X_e \), then

\[
k_+(A_o - X_e) = k_-X_e = 0
\]  \hspace{1cm} (Eq. 5)

which rearranges to give

\[
k_- = \frac{k_+(A_o - X_e)}{X_e}
\]  \hspace{1cm} (Eq. 6)

Substitution of Equation 6 into Equation 4 gives rise to

\[
\frac{dX}{dt} = \frac{k_+A_o}{X_e} (X_e - X)
\]  \hspace{1cm} (Eq. 7)

which on integration and making use of the fact that \( X = 0 \) when \( t = 0 \) yields:

\[
k_+ = \frac{X_e}{A_o t} \ln \frac{X_e}{X_e - X}
\]  \hspace{1cm} (Eq. 8)

Equation 5 rearranges to

\[
\frac{X_e}{A_o} = \frac{k_+}{k_+ + k_-}
\]  \hspace{1cm} (Eq. 9)

and substitution into Equation 8, followed by rearrangement,
yields:

\[ k_+ + k_- = \frac{1}{t} \ln \frac{X_e}{X_e - X} \]  
(Eq. 10)

Let \( k_+ + k_- = k \) and rearrangement of Equation 10 gives:

\[ \ln(X_e - X) = -kt + \ln X_e \]  
(Eq. 11)

Taking antilogs of Equation 11 and rearranging gives:

\[ X = X_e - X_e e^{-kt} \]  
(Eq. 12)

Starting with Equation 12 Carstensen, et al. (72) drew a crude curve through the data points obtained from a plot of \( X \) versus \( t \) for the vitamin E succinate degradation. They evaluated \( k \) and \( X_e \) by substituting values for \( t \) and \( X \), taken from the crude curve, into Equation 12. The time intervals used were 2, 4, and 6 hours, but any arithmetical series could have been used (e.g., 1, 2, and 3, or 3, 6, and 9). The highest numbers compatible, with the data, give the best estimates.

For the time intervals 2, 4, and 6:

\[ X_2 = X_e - X_e e^{-2k} \]  
(Eq. 13)

\[ X_4 = X_e - X_e e^{-4k} \]  
(Eq. 14)

\[ X_6 = X_e - X_e e^{-6k} \]  
(Eq. 15)
These equations yielded in turn the following working equations:

\[ e^{-2k'} + e^{-2k} = 1 + e^{-2k} = \frac{X_6 - X_4}{X_4 - X_2} \]  
(Eq. 16)

or \[ e^{-2k} = \frac{X_6 - X_4}{X_4 - X_2} \]  
(Eq. 17)

\( e^{-2k'} \) and \( e^{-2k} \) are roots of a quadratic equation with \( e^{-2k'} = 1 \) here. \( e^{-2k} \) can be calculated from Equation 17 and hence the rate constant \( k \) can be found. Substitution of the value for \( e^{-2k} \) into Equation 16 will give the value of \( e^{-2k'} \). An estimate of how good the crude curve was can be found by comparing the value of \( e^{-2k'} \) to 1.0. If this root is 1.0 or very close to it, then the initial estimate of \( X_2, X_4 \) and \( X_6 \) and the resulting value for the rate constant \( k \) are justified. If \( e^{-2k'} \) is not close to 1.0 the curve is redrawn and the calculation repeated. Insertion of the value for \( e^{-2k} \) into Equation 13 will yield the equilibrium value \( X_e \). The equation for the theoretical curve can therefore be estimated.
**EXPERIMENTAL**

**General**

In order to investigate the effect of pressure on solid-solid interactions, it was necessary to assume that if an interaction occurred in the molecular mixture, with or without pressure, then, the complex or complexes formed should have different thermal characteristics to those of the original mixture. It was, therefore, necessary to be able to compare the molecular mixture and the compressed mixture with that of a standard, i.e., a complex of known stoichiometry, so that any similarities or differences might indicate whether or not complexation had taken place. Infrared and X-ray diffraction spectroscopy were tried as methods of analysis before TGA and DSC were decided upon.

**Differential Scanning Calorimetry (DSC)**

The Dupont 900* Differential Thermal Analyzer, with a built-in x-y recorder,** was used, in conjunction with a DSC cell, to run all DSC thermograms. The DSC cell constant (E) was determined from the heat of fusion of indium. The samples, which ranged in weight from 3.5-5 mg

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*Dupont Instruments, Wilmington, Delaware 19898.
**Hewlett-Packard, Moseley Division, Pasadena, California.
(weighed to ±0.005 mg), were heated in aluminum pans in an air atmosphere at a rate of 10°C/min from ambient temperature to either 200°C or 250°C, depending on the sample being studied. Before analysis each of the compressed samples was powdered by grinding in a mortar. The enthalpies were determined by measurement of the peak areas with a Keuffel and Esser Compensating Polar Planimeter, model 62.0000, and substitution of this area into Equation 1, page 17.

Thermogravimetric Analysis (TGA)

TGA thermograms were run on the Dupont 950 Thermo-gravimetric Analyzer plug-in module for the Dupont 900 Differential Thermal Analyzer. The sample size was 9-10 mg (weighed to ±0.0005 mg) and 8-9 mg were suppressed so that a weight loss sensitivity of 0.2 mg/in. could be used. Each sample was heated in a platinum pan, at a rate of 10°C/min, from ambient temperature to 200°C, under nitrogen, which was used at a flow rate of 850 ml/min as purge gas.

Compressed samples were powdered by grinding in a mortar before analysis. Both TGA and DSC analyses were carried out on portions of the same sample.
Reagents

The following reagents were used:

\[ \text{p-aminobenzoic acid M.W. 137.14} \]
\[ \text{cat. no. 14 Eastman Organic Chemicals;} \]

\[ \text{m-aminobenzoic acid M.W. 137.14} \]
\[ \text{cat. no. 633 Eastman Organic Chemicals;} \]

\[ \text{anthranilic acid M.W. 137.14} \]
\[ \text{cat. no. 29 Eastman Organic Chemicals;} \]

\[ \text{succinamic acid M.W. 117.10} \]
\[ \text{Aldrich Chemical Co., Inc.;} \]

\[ \text{oxalic acid, anhydrous M.W. 90.04} \]
\[ \text{cat. no. 197 Eastman Organic Chemicals;} \]

\[ \text{oxalic acid, dihydrate M.W. 126.07} \]
\[ \text{cat. no. ACS 1141 Allied Chemical, General} \]
\[ \text{Chemical Division;} \]

\[ \text{caffeine M.W. 194.19} \]
\[ \text{cat. no. 355 Eastman Organic Chemicals.} \]

I. Preparation of Solid Complexes

A. \text{m-Aminobenzoic Acid: Oxalic Acid Complex}

During complexation studies, carried out by Wurster and Kildsig (62), it was noted that an interaction occurred between solutions of \text{m-aminobenzoic acid} and \text{oxalic acid}, resulting in the formation of a precipitate. It was decided to duplicate their observation.

Equal volumes of saturated solutions of \text{m-aminobenzoic acid (MABA)} and \text{oxalic acid} were mixed together and agitated for 24 hours. A precipitate resulted
which after collection and thorough washing with distilled water was allowed to dry in air at room temperature. When dry, the precipitate was placed in a glass screw-capped container, sealed with plastic tape and stored in a desiccator over anhydrous calcium sulfate.

In order to find the composition of the precipitate, it was necessary to find the concentration of each acid in its saturated solution, and also the concentration of each acid remaining in the mixture of solutions after separation of the precipitate. The saturated oxalic acid solution and the mixed acid solution was assayed using N/2 sodium hydroxide solution. The MABA was assayed in both the mixture and saturated solution using an Aminco Bowman spectrofluorimeter* with activating light at 315 μm and fluorescence observed at 410 μm (63). A borate buffer of pH 8.6 (63) was used to make all dilutions and to obtain maximum fluorescence.

From the differences between the initial and final concentrations of each acid it was possible to calculate the stoichiometry of the complex. In order to ascertain whether or not the complex contained water of hydration the complex was sent out for elemental assay. A DSC thermogram was also run on the complex.

Attempts were made to obtain other complexes by the above method of preparation.

*American Instrument Co., Silver Spring, Maryland.
B. p-Aminobenzoic Acid:Oxalic Acid Complex

Saturated solutions of PABA and oxalic acid were mixed and the above procedure followed. Volumetric and spectrofluorimetric analysis (activating light 295 mp - fluorescence 345 mp) were used to obtain the stoichiometry of the resulting complex. An elemental assay was performed and a DSC thermogram was run on this complex.

Subsequent analyses of solid complexes were carried out using elemental analysis only in conjunction with DSC thermograms.

C. o-Aminobenzoic Acid:Oxalic Acid Complex

Saturated solutions of o-aminobenzoic acid and oxalic acid were mixed as above.

D. Caffeine:p-Aminobenzoic Acid Complex

Saturated solutions of PABA and caffeine were mixed as before. The resulting precipitate was air dried for 24 hours. A portion of this was dried at 70°C for 3 hours. DSC and TGA thermograms were run and elemental analysis performed on both samples to determine their stoichiometry.

E. Interactions Between (a) m-Aminobenzoic Acid and (b) p-Aminobenzoic Acid With Succinamic Acid

Wurster and Kildsig (62) also noted that an interaction occurred between succinamic acid and
\( m \)-aminobenzoic acid. In the attempt to prepare further complexes, saturated solutions of the above acids were treated as before. Elemental analyses were performed on both resulting precipitates and DSC thermograms were also run. Nmr, ir and melting point measurements were also made on these precipitates.


A. Recrystallization from Water

The complex was dissolved in hot water and allowed to cool. When cold the crystals were filtered off, washed with distilled water, and allowed to dry in the air. When dry, a DSC thermogram was run and compared with that of the original complex.

B. Recrystallization from 95% Ethanol

The complex was dissolved in hot 95% ethanol. When cool, the crystals were filtered off and dried in the air. A DSC thermogram was run and compared with that of the original complex. A sample was sent out for elemental assay to determine its stoichiometry.

C. Drying to Constant Weight

The 1:1: complex was dried at 60°C over phosphorus pentoxide to constant weight. Elemental analysis was
performed on the residue and its stoichiometry determined. A DSC thermogram was made and compared with that of the original complex.

D. Exposure of Dried Complex to Water

The dried residue was placed under a bell jar together with a beaker of water for 24 hours. At the end of this time, a DSC thermogram was run and compared with that of the original 1:1:1 complex.

E. The Effect of Pressure on the 1:1:1 Complex

50 mg samples of the complex were compressed at varying pressures from 250 lb. to 3000 lb. using a 3/16" punch and die for 5 minutes. DSC thermograms were run for each tablet, after it had been broken up in a mortar, and compared to that of the original complex. An elemental assay was performed on a high pressure sample and its stoichiometry determined.

III. Compressional Studies

Procedure

All samples were compressed using a Carver Laboratory Press, model B, and a specially designed compression block (Figure 1).
Preparation of Molecular Mixtures

Weighed amounts of PABA and anhydrous oxalic acid were ground together in a mortar and the required amount of water was added by pipet and triturated well with the two acids. The mixture was then transferred to a screw-capped glass vial, sealed with water-proof plastic tape to exclude the transport of water in or out, and allowed to equilibrate for 48 hours at room temperature. The molecular mixtures used are shown in Table I.

TABLE I
Composition of Molecular Mixtures

<table>
<thead>
<tr>
<th>Mixture stoichiometry</th>
<th>Composition of Mixture</th>
<th>GMS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PABA</td>
<td>Anhyd Oxalic</td>
</tr>
<tr>
<td>1:1:1</td>
<td>3.04</td>
<td>2.0</td>
</tr>
<tr>
<td>1:1:1.5</td>
<td>3.04</td>
<td>2.0</td>
</tr>
<tr>
<td>1:1:2</td>
<td>3.04</td>
<td>2.0</td>
</tr>
<tr>
<td>1:1:3</td>
<td>3.04</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Compression of Molecular Mixtures

After equilibration, approximately 250 mg of mixture were weighed and placed into a 3/8" diameter die in the specially designed compression block (Figure 1) and compressed at a particular pressure for a definite time.
A - Tablet
B - Die
C - Upper punch
D - Lower punch
E - Upper punch holder
F - Lower punch and die holder
G - Hollow upper punch holder
H - Ejection plunger

Figure 1. Compression block assembly (4/5 actual size).
The tablet was pressure ejected from the die (Figure 1), and placed in a screw-capped glass vial and sealed as above with plastic tape. After standing for various time intervals, usually zero, one, two, three, four, five, six, seven, and 48 hours, tablets were ground in a mortar and DSC and TGA thermograms were run on each sample. Times of compression varied from a few seconds up to ten minutes and pressures from 1000 pounds to 20,000 pounds.

A. Determination of the Effect of Various Amounts of Water on Complex Formation Under Pressure

Molecular mixtures were prepared with the compositions shown in Table I and compressed at 5000 pounds for ten minutes using a 3/8" punch and die set. The initial compressed sample of each mixture was broken up immediately after it was ejected from the die, and subsequent samples were broken up at hourly intervals, up to seven hours, from the time of ejection. An additional sample was broken up at 48 hours. DSC thermograms were run on all compressed samples and also on the 48-hour aged mixture.

As DSC thermograms showed endothermic peaks at different temperatures for the various molecular mixtures, the comparison had to be done pictorially rather than mathematically.
B. Comparison of Compressed Mixture with the 1:1:1 Known Complex

The 48-hour, 10-minute compressed mixture from above was recompressed at 10,000 lbs. for ten minutes. Also, the known 1:1:1 complex was treated similarly. DSC thermograms were run on samples of each and compared. The recompressed sample of the mixture was divided into two parts (150 mg each). To one part a drop of water was added and then both parts were compressed separately at 5,000 lbs. for ten minutes. The compressed known 1:1:1 complex was treated similarly. DSC thermograms were run on all samples and compared.

C. Determination of the Effect of Various Pressures on the 1:1:2 PABA:Oxalic Acid:Water Molecular Mixture on Complex Formation

The previous experiment indicated that the 1:1:2 mixture would be suitable for this study. Separately prepared samples of this mixture were compressed at various pressures for ten minutes using a 3/8" punch and die set. The pressures employed were 1000, 2000, 3000, 5000 and 20,000 lbs. The tablets were broken up at the same intervals as before with the addition of 96 and 176 hours for the 1000 pound samples and 120 hours for the 2000 pound samples. TGA and DSC thermograms were run for each hourly sample. The weight changes associated with each DSC peak were determined from the TGA thermograms and the enthalpy
changes from the DSC thermograms. Weight versus time, enthalpy versus time, log weight versus time, and log enthalpy versus time plots were utilized to treat the data generated for each peak.

D. Determination of the Effect of Differing Compression Times on Complex Formation

The 1:1:2 PABA, oxalic acid and water molecular mixture was compressed at 5000 pounds using a 3/8" punch and die set for various times from just bringing the sample up to 5000 pounds and then releasing it immediately, to ten minutes duration. Tablets were broken up hourly as before and the data treated in a similar manner to the previous experiment.
RESULTS AND DISCUSSION

I. Preliminary Studies

A. m-Aminobenzoic Acid:Oxalic Acid Complex

The stoichiometry of this complex was found to be 2 moles MABA:1 mole oxalic acid (Table II) by the combination titration and spectrofluorimetric method. Elemental analysis confirmed the 2:1 ratio and also indicated that the complex was anhydrous (Table III). The DSC thermogram contained only one endothermic peak at 250°C, the area of which is proportional to the heat of fusion (Figure 2).

B. p-Aminobenzoic Acid:Oxalic Acid Complex

The stoichiometry of this complex was found to be 1 mole PABA:1 mole oxalic acid by the combination titration and spectrofluorimetric method of analysis. Elemental analysis showed that the complex also contained water and that the true stoichiometry was 1 mole PABA:1 mole oxalic acid:1 mole water (Tables II and III). The DSC thermogram indicates five endothermic peaks with maxima at 100-105°C, 160-165°C, 200°C, 215°C and 235°C. The nature of these peaks will be discussed later. For convenience, the first two peaks will be referred to as the 105°C and the 165°C peaks, respectively.
### TABLE II
Complex Stoichiometries

<table>
<thead>
<tr>
<th>System</th>
<th>Stoichiometry of Complex</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A : B : H₂O</td>
</tr>
<tr>
<td><strong>m-Aminobenzoic acid</strong></td>
<td>2 : 1</td>
</tr>
<tr>
<td>Oxalic acid</td>
<td></td>
</tr>
<tr>
<td><strong>p-Aminobenzoic acid</strong></td>
<td>1 : 1 : 1</td>
</tr>
<tr>
<td>Oxalic acid</td>
<td></td>
</tr>
<tr>
<td><strong>α-Aminobenzoic acid</strong></td>
<td>no interaction</td>
</tr>
<tr>
<td>Oxalic acid</td>
<td></td>
</tr>
<tr>
<td><strong>p-Aminobenzoic acid</strong></td>
<td>1 : 1 : 3</td>
</tr>
<tr>
<td>Caffeine</td>
<td></td>
</tr>
<tr>
<td><strong>p-Aminobenzoic acid</strong></td>
<td>1 : 1</td>
</tr>
<tr>
<td>Caffeine, after drying</td>
<td></td>
</tr>
<tr>
<td><strong>p-Aminobenzoic acid</strong></td>
<td>chemical reaction</td>
</tr>
<tr>
<td>Succinamic acid</td>
<td>resulting in</td>
</tr>
<tr>
<td>m-Aminobenzoic acid</td>
<td>compound formation</td>
</tr>
<tr>
<td>Sample</td>
<td>Percentage</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>------------</td>
</tr>
<tr>
<td></td>
<td>C  H  N</td>
</tr>
<tr>
<td>MABA:Oxalic acid complex</td>
<td>52.30 4.41</td>
</tr>
<tr>
<td></td>
<td>52.30 4.41</td>
</tr>
<tr>
<td><strong>MEAN</strong></td>
<td>52.30 4.41</td>
</tr>
<tr>
<td>PABA:Oxalic acid: Water complex</td>
<td>43.80 4.53</td>
</tr>
<tr>
<td></td>
<td>43.96 4.53</td>
</tr>
<tr>
<td><strong>MEAN</strong></td>
<td>43.88 4.53</td>
</tr>
<tr>
<td>PABA:Caffeine: Water complex</td>
<td>47.59 5.81</td>
</tr>
<tr>
<td></td>
<td>47.69 5.86</td>
</tr>
<tr>
<td><strong>MEAN</strong></td>
<td>47.64 5.83</td>
</tr>
<tr>
<td>PABA:Caffeine complex</td>
<td>54.17 5.15</td>
</tr>
<tr>
<td></td>
<td>54.35 5.17</td>
</tr>
<tr>
<td><strong>MEAN</strong></td>
<td>54.26 5.16</td>
</tr>
<tr>
<td>PABA/Succinamic acid reaction product</td>
<td>55.78 4.68</td>
</tr>
<tr>
<td></td>
<td>55.75 4.66</td>
</tr>
<tr>
<td><strong>MEAN</strong></td>
<td>55.77 4.67</td>
</tr>
<tr>
<td>Sample</td>
<td>Percentage</td>
</tr>
<tr>
<td>------------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>MABA/Succinamic acid reaction product</td>
<td></td>
</tr>
<tr>
<td></td>
<td>55.21</td>
</tr>
<tr>
<td></td>
<td>55.30</td>
</tr>
<tr>
<td>MEAN</td>
<td>55.25</td>
</tr>
</tbody>
</table>
Figure 2. DSC thermogram of the 2:1 MABA:oxalic acid complex.
Figure 3. DSC thermograms showing effect of recrystallizing the 1:1:1 complex from 95% ethanol.
C. p-Aminobenzoic Acid (OABA): Oxalic Acid Complex

No precipitate resulted when the saturated solutions of anthranilic acid and oxalic acid were mixed, even after standing for one month (Table II). It is interesting to note here the differences between the three aminobenzoic acids. MABA forms a 2:1 solid complex with oxalic acid, PABA forms a 1:1:1 solid complex with oxalic acid and water from aqueous solution while OABA forms no solid complex. Either OABA forms a soluble complex or none at all, due perhaps to strong intramolecular hydrogen bonding occurring between the adjacent carbonyl and amino groups.

D. Caffeine:p-Aminobenzoic Acid Complex

Elemental analysis of the 24 hour air dried complex indicated a stoichiometry of 1 mole PABA: 1 mole caffeine: 3 moles of water. After drying this complex at 70°C for three hours, elemental analysis indicated a stoichiometry of 1 mole PABA: 1 mole caffeine (Tables II and III). All the water had been removed. The DSC thermogram of the 1:1:3 complex had three peak maxima at 60°C, 132°C and 260°C, while the 1:1 complex had two peak maxima at 135°C and 260°C (Figure 4). A DSC thermogram of a sample of the 1:1:3 complex, which had been standing 9 months, had lost the 60°C peak and had the same DSC thermogram as that of the 70°C dried crystals. The TGA
thermogram for the 1:1:3 complex indicated a 14% weight loss between ambient temperature and 135°C, whereas the 9-month and 70°C-dried 1:1 samples showed no weight loss over the range. A 14% weight loss from the 1:1:3 complex corresponded to 3 moles of water.

On the basis of this information the peaks can be assigned. The 60°C peak was due to dissolution of the 1:1:3 complex in its water of hydration which was subsequently removed. The 132°-135°C peak was where the melting point of the anhydrous complex occurred; the 260°C peak was due to decomposition of the 1:1 complex. Photomicrographs of the three caffeine complexes, which were mounted in mineral oil, are shown in Figure 5.

The above 1:1:3 stoichiometry does not agree with that found by Higuchi and Lach (79,80) who showed the isolable complex to consist of 1 mole PABA:1 mole caffeine. The complex in this study was prepared by both their method and by the method previously described in the experimental section. They arrived at their value for the stoichiometry by the method of solubility analysis which would not indicate the presence of water, and not by elemental assay, TGA or DSC. The melting point of the 1:1:3 complex was found to be 70-71°C which was in agreement with the value they found. The melting points of the anhydrous 1:1 complexes (9 months and 3 hours at 70°C) were both found to be 133-134°C.
Figure 5. Photomicrographs of PABA:caffeine complexes.
E. Interactions Between (a) m-Aminobenzoic Acid and (b) p-Aminobenzoic Acid with Succinic Acid

Elemental analysis (Table III) yielded the same empirical formulas for the reaction products of both (a) and (b). The noted difference between these formulas and the expected formulas was that each was lower by one \(-\text{NH}_3\) group. Nmr*, ir (see Appendix) and melting points indicated that the meta acid yielded N-(3-carboxyphenyl)-succinic acid and the para acid yielded N-(4-carboxyphenyl)-succinic acid. The probable reaction proceeds via the initial hydrolysis in acid solution of the amide of succinic acid with the formation of succinic acid. The reaction then most probably continues via the mechanism put forward by Higuchi, et al. (81-83), whereby the succinic acid forms some anhydride which then reacts with the amine part of the amino acid to form the appropriate succinic acid (Figure 6).

A sample of N-(4-carboxyphenyl)-succinic acid was obtained (from Aldrich cat. no. S38150-0) and compared with the above two compounds. The nmr indicated that the purchased sample was impure although its melting point was close to that of the literature value. The melting point of the N-(4-carboxyphenyl) compound was above the literature value, whereas the N-(3-carboxyphenyl) compound was the same as the literature value (Table IV).

*The nmr work was done by Bruce Stein and Matthew Suffness.
Figure 6. Possible reaction mechanism for the reaction between (a) PABA and (b) MABA with succinamic acid.
### TABLE IV
Melting Points of Succinamic Acid Reaction Products with (a) PABA and (b) MABA

<table>
<thead>
<tr>
<th>Compound</th>
<th>Melting Point</th>
<th>Literature Value Melting Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-(3-Carboxyphenyl)-succinamic acid</td>
<td>232-234°C</td>
<td>232°C</td>
</tr>
<tr>
<td>N-(4-Carboxyphenyl)-succinamic acid</td>
<td>239-241°C</td>
<td>225-226°C</td>
</tr>
<tr>
<td>Aldrich no. S38150-0</td>
<td>223-224°C</td>
<td></td>
</tr>
</tbody>
</table>


A. Recrystallization from Water

After recrystallization of the 1:1:1 complex from water, and subsequent drying, its thermogram was identical with the one run before recrystallization. Therefore, it can be concluded that this complex is unaffected by recrystallization from water and would appear to be the favored form under aqueous conditions.

B. Recrystallization of 1:1:1 Complex from 95% Ethanol

On recrystallization from 95% ethanol, the DSC thermogram of the crystalline material was completely different from that of the 1:1:1 complex (Figure 3).
Elemental analysis (Tables V and VI) showed the stoichiometry of the crystals to be 2 moles PABA:1 mole oxalic acid and that this complex was also anhydrous. The reaction involves:

\[2 \text{ moles } 1:1:1 \text{ complex } \rightarrow 1 \text{ mole } 2:1 \text{ complex.}\]

This complex had the same stoichiometry as that of the \(m\)-aminobenzoic acid-oxalic acid complex.

**TABLE V**

Complex Stoichiometries

<table>
<thead>
<tr>
<th>System</th>
<th>Stoichiometry</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) 12-Aminobenzoic acid/Oxalic acid/H(_2)O complex</td>
<td>1 : 1 : 1</td>
</tr>
<tr>
<td>(2) (1) recrystallized from 95% ethanol</td>
<td>2 : 1</td>
</tr>
<tr>
<td>(3) (1) dried to constant weight at 60°C over P(_2)O(_5)</td>
<td>1 : 1</td>
</tr>
<tr>
<td>(4) (1) compressed at 20,000 lbs.</td>
<td>1 : 1 : 1</td>
</tr>
<tr>
<td>Complex</td>
<td>Percentage</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>------------</td>
</tr>
<tr>
<td></td>
<td>C  H  N  O</td>
</tr>
<tr>
<td>PABA: Oxalic Acid: Water complex</td>
<td></td>
</tr>
<tr>
<td>Recrystallized from 95% ethanol</td>
<td>52.84 4.41 7.75 35.00</td>
</tr>
<tr>
<td></td>
<td>52.69 4.47 7.74 35.10</td>
</tr>
<tr>
<td><strong>MEAN</strong></td>
<td>52.77 4.44 7.74 35.05</td>
</tr>
<tr>
<td>Dried to constant weight over P₂O₅</td>
<td>47.37 4.02 6.17 42.44</td>
</tr>
<tr>
<td>at 60°C</td>
<td>47.57 3.95 6.08 42.40</td>
</tr>
<tr>
<td><strong>MEAN</strong></td>
<td>47.47 3.99 6.12 42.42</td>
</tr>
<tr>
<td>Compressed at 20,000 lbs.</td>
<td>44.12 4.45 5.71 45.72</td>
</tr>
<tr>
<td></td>
<td>44.27 4.49 5.73 45.51</td>
</tr>
<tr>
<td><strong>MEAN</strong></td>
<td>44.495 4.47 5.72 45.61</td>
</tr>
</tbody>
</table>
C. Drying to Constant Weight

After drying to constant weight, both the 105°C and the 160-165°C peaks had disappeared (Figure 7) from the DSC thermogram. Elemental analysis (Table VI) showed this residue to have a stoichiometry of 1 mole PABA: 1 mole oxalic acid (Table V). One mole of water had been removed on drying. The thermogram of the dehydrate was completely different from that of a 1:1 molecular mixture of PABA and oxalic acid indicating that the dehydrate was still complexed. The conclusions that were made from the above results were that the 105°C and the 165°C peaks were both due to water and that water existed in two different states in the 1:1:1 complex.

D. Exposure of Dried 1:1:1 Complex to Water Vapor

On exposure to water vapor, the dried complex took up water at the 105°C peak position to a greater extent than before (Figure 7), but none was taken up at the 165°C peak position. This further indicated that water in the 105°C and 165°C positions was bound differently.

E. The Effect of Pressure on the 1:1:1 Complex

The effect of pressure on the 1:1 complex is demonstrated in Figure 8. As the pressure was increased, the area under the 105°C peak increased, while that of the 165°C peak decreased. At between 2000-3000 lbs., the 165°C
Figure 7. Effect of drying 1:1:1 complex to constant weight and subsequent exposure to water vapor.

A - 1:1 molecular mixture
B - dried complex exposed to water vapor
C - 1:1:1 complex dried to constant weight → 1:1 complex
D - 1:1:1 complex
Figure 8. Effect of pressure on the 1:1:1 complex using 3/16" punch and compression time of 5 mins.
peak had virtually disappeared. Elemental analysis showed that the stoichiometry had not changed. One mole of water was still present after high pressure treatment (Tables V and VI).

It was obvious from the above data that pressure altered the state in which water was bound in the complex. Sood and Stager (45), as mentioned earlier, had shown that high pressures applied to inorganic hydrates brought about either dehydration or irreversible phase transformations. A similar situation seems to exist here with an organic hydrate, namely the 1:1:1 complex. It will be shown later that reversal of the above system can be brought about by the use of high pressure and moisture.

Nmr spectra (see Appendix A) run on all the oxalic acid complexes with PABA and MABA, and subsequent integration of these spectra, accounted for all the protons that would be expected if the molecules of the complexes were physically bound. Exchange of -OH and -NH protons by deuterons also indicated that the complex molecules were physically bound.

Infrared spectra (see Appendix B) showed differences between the different complexes, and indicated hydrogen bonding in all by the presence of broad bands due to -NH and -OH overlap, stretching from 2.9-4.8 μ. Virtually no differences between the compressed and uncompressed 1:1:1 PABA:oxalic acid:water complex occurred; other than that the uncompressed complex showed sharper peak definition.
(see Appendix B). Both the 1:1 and the 2:1 PABA:oxalic acid anhydrous complexes showed narrower bands in the \(-\text{OH}, -\text{NH}\) hydrogen bonding region stretching from 3.1–4.8 \(\mu\) (see Appendix B). The narrowing of the band in the anhydrous complexes is not unexpected since the variety of different kinds of hydrogen bonds has been decreased with the removal of water.

III. Compressional Studies on Mixtures of PABA, Oxalic Acid and Water

In the following studies only the thermograms of the 105°C and the 165°C peaks will be shown, as these are the only ones in which changes occur.

A. Effect of Pressure on Various Mixtures of PABA, Oxalic Acid and Water

Molecular mixtures containing varying amounts of water, as shown in Table I, were prepared as previously described and compressed at 5,000 lbs. for 10 minutes. DSC thermograms of the four equilibrated mixtures are shown in Figure 9. The thermograms were similar, with the exception of the 1:1:1 mixture, and contained one major endothermic peak at 100°C–105°C in the temperature range 50°C to 190°C. The 1:1:1 mixture had five endothermic peaks in this temperature range at 70°C, 90°C, 145°C, 185°C and 195°C. The initial effect of pressure on these mixtures is shown in Figure 10 where the definition of the
Figure 9. Comparison of uncompressed molecular mixtures of PABA, oxalic acid and water.
Figure 10. DSC thermograms showing initial effect of 5000 lb. pressure on molecular mixtures of PABA, oxalic acid and water.
105°C peak became sharper in the 1:1:1.5, 1:1:2 and 1:1:3 mixtures. The most obvious change occurred in the 1:1:3 mixture which showed a small peak at 165°C. A very small additional peak occurred in the 1:1:1 mixture at 165°C.

Figures 11 through 18 show the effect of allowing the compressed mixtures to stand for various times before powdering and running DSC thermograms. The thermograms of the 1:1:1 H₂O and the 1:1:1.5 H₂O mixtures did not change even after standing 48 hours. A peak at 165°C appeared in the 1:1:2 mixture 1 hour sample; continued to increase in area rapidly until 4 hours after compression; and had reached a maximum by about 7 hours (Figure 17) as evidenced by the 48-hour sample (Figure 18). The 165°C peak of the 1:1:3 mixture increased rapidly until 3 hours after compression, also reaching a maximum by about 7 hours (Figure 17) as evidenced by its 48-hour sample. The 100°C-105°C peak decreased in area for the 1:1:2 and the 1:1:3 mixtures as the 165°C peak area increased.

The changes in the two peaks indicated that the way in which water was bound in the uncompressed mixture had been altered by compression and was time dependent. The thermograms also showed that the rate of formation of the 165°C peak, and the rate of decrease of the 105°C peak, varied with the amount of water present in the mixture. The changes in the 1:1:3 mixture were faster than those in the 1:1:2 mixture. No changes occurred in the 1:1:1.5 mixture which had a similar initial thermogram to the
Figure 11. DSC thermograms showing effect of 5000 lb. pressure, 1 hour after compression, on molecular mixtures of PABA, oxalic acid and water.
Figure 12. DSC thermograms showing effect of 5000 lb. pressure, 2 hours after compression, on molecular mixtures of PABA, oxalic acid and water.
Figure 13. DSC thermograms showing effect of 5000 lb. pressure, 3 hours after compression, on molecular mixtures of PABA, oxalic acid and water.
Figure 14. DSC thermograms showing effect of 5000 lb. pressure, 4 hours after compression, on molecular mixtures of PABA, oxalic acid and water.
Figure 15. DSC thermograms showing effect of 5000 lb-pressure, 5 hours after compression, on molecular mixtures of PABA, oxalic acid and water.
Figure 16. DSC thermograms showing effect of 5000 lb. pressure, 5 hours after compression, on molecular mixtures of PABA, oxalic acid and water.
Figure 17. DSC thermograms showing effect of 5000 lb. pressure, 7 hours after compression, on molecular mixtures of PABA, oxalic acid and water.
Figure 18. DSC thermograms showing effect of 5000 lb pressure, 48 hours after compression, on molecular mixtures of PABA, oxalic acid and water.
1:1:2 and the 1:1:3 mixtures. It would appear, then, that a minimum amount of water was necessary before any interaction could occur, under pressure, in the PABA:oxalic acid:water mixtures and that this quantity is somewhere between 1.5 and 2 moles for 1 mole each of PABA and oxalic acid. The difference between the 1:1:1 uncompressed mixture thermogram and those of the other three would tend to indicate that some type of interaction or orientation of molecules had occurred in the equilibrated mixtures containing more than one mole of water.

The 1:1:2 mixture was chosen to be used in subsequent experiments because it showed time dependent changes when compressed; also, when ground up immediately after compression, it showed no peak at 165°C, so that at zero time after compression there would be no peak area at 165°C. It was noticed that when the 1:1:2 and the 1:1:3 mixtures were compressed that water was squeezed out of the mixture and ran down the sides of the bottom punch.

B. Comparison of the 48-Hour 1:1:2 Compressed Mixture With the 1:1:1 Known Complex

The thermogram of the known 1:1:1 complex (A) and that of the 48-hour 1:1:2 compressed mixture (C) are shown in Figure 19. The thermograms have corresponding peaks at 105°C and 165°C. On compression at 10,000 lbs., the thermogram of A changed to B and that of C changed to D. The effect of pressure was to remove the 165°C peak and
Figure 19. DSC thermograms showing effect of compressing 1:1:1 complex and recompressing the compressed 1:1:2 mixture (48-hour sample). A - 1:1:1 complex; B - 1:1:1 compressed complex; C - 1:1:2 compressed mixture (48-hour sample); D - recompressed 1:1:2 compressed mixture.
increase the size of the 105°C peak. In Figure 20, E and G are the thermograms of B and D, respectively, after portions of B and D were mixed with a drop of water and recompressed at 5,000 lbs. for 10 minutes. It is evident from the thermograms that the 165°C peak had reappeared and that the 105°C peak had decreased in area. F and G (Figure 20) represent portions of B and D, respectively, that were recompressed without the addition of water, and it is evident that no changes occurred on recompression.

It has been shown that compression of an organic hydrate (1:1:1 complex) brought about a phase transformation similar to that of Sood and Stager (45) for inorganic hydrates. In addition, it was shown that the reaction was reversible under pressure if water was added to the mixture before recompression. In the case of the 1:1:2 mixture, it has been shown that time dependent changes occurred, in the way in which water was bound in the mixture, after compression. The 1:1:2 mixture converted to the 1:1:1 complex after excess water had been squeezed from it under pressure. Also, the 48-hour sample of the compressed mixture and the 1:1:1 complex underwent a series of identical changes.

**X-Ray Diffraction Spectra**

X-ray diffraction patterns were run on the compressed and uncompressed samples of the PABA:oxalic acid complexes

*The X-ray work was performed by Mr. Karl G. Zipple of the Upjohn Company.*
Figure 20. DSC thermograms showing effect of adding water to compressed samples B and D after grinding, which yield E and G, respectively, after recompression. H and F show effect of recompression of B and D without addition of water.
and the 1:1:2 mixtures. Although this analytical method did not provide a quantitative method for studying solid state interactions, it did, however, provide some interesting data which correlate well with the DSC thermograms.

Figure 21 shows the differences that occur in the peak intensities for the 1:1:1 uncompressed (I) and compressed (II) complexes, indicating structural differences. The X-ray patterns of the compressed complex (II) and the 1:1:2 uncompressed mixture (III) resemble each other, as do their DSC thermograms. This would seem to indicate that compression of the complex alters its structure to one close to that of the 1:1:2 mixture. Preliminary X-ray studies on the compressed 1:1:2 mixture, tend to also show that changes occur between the molecules of this mixture on compression. Further work is necessary utilizing similar time intervals to those employed in the TGA and DSC experiments.

Figure 22 compares the X-ray patterns of the 1:1:1 complex (I), the 1:1:1 dried complex (1:1) (IV) and the 2:1 complex (V). These spectra are all very different from each other, as are their DSC thermograms, indicating that each has a definite structure of its own.
Figure 21. X-ray diffraction patterns of PABA:oxalic acid:water complexes. I - 1:1:1 complex; II - 1:1:1 compressed complex; III - 1:1:2 mixture.
Figure 22. X-ray diffraction patterns of PABA:oxalic acid:water complexes. I - 1:1:1 complex; IV - 1:1 anhydrous complex; V - 2:1 anhydrous complex.
Calculation of the DSC Cell Constant E

E was found by substituting the following values into the equation (Equation 1, page 17):

\[ \Delta H = \frac{E \cdot \Delta T_s \cdot T_s \cdot A}{M \cdot a} \]  \hspace{1cm} (Eq. 1)

\( \Delta H_{\text{fusion}} \) for indium = 6.7 mcal/mg; \( a = 1.5 \) sq.in.;
\( \Delta T_s = 0.5^\circ C/\text{in.}; \ T_s = 10^\circ C/\text{in.}; \ M = 15.51 \) mg and
\( a = 10^\circ C/\text{min.} \). The value of \( E \) was calculated to be
141 mcal/\(^\circ C\)-min, and was used in subsequent enthalpy calculations using the above equation.

For all the following DSC runs the value of \( E \) was 141 mcal/\(^\circ C\)-mg; \( \Delta T_s = 0.2^\circ C/\text{in.}; \ T_s = 20^\circ C/\text{in.}; \) and
\( a = 10^\circ C/\text{min.} \). Substitution of these values into Equation 1 gives:

\[ \Delta H \text{ mcal/mg} = \frac{56.4 A}{M} \]  \hspace{1cm} (Eq. 2)

In the following two studies all points on linear graphs were plotted with their standard deviations taken from at least three separate runs. The semilogarithmic plots were derived from these curves.
C. The Kinetic Effect of Various Pressures, on the 1:1:2 PABA:Oxalic Acid:Water Molecular Mixture, on Complex Formation

Figures 23 through 26 show the effect of pressure on the weight of water associated with the 105°C and 165°C endothermic DSC peaks. The data were obtained from the TGA thermograms (weight loss versus temperature) and plotted as percentage w/w of water (of the sample weight) associated with the endothermic peaks versus time. The sample compressed at 1,000 lbs. (Figure 23) showed no discernible weight changes for the first seven hours, and it was not until 48 hours that any weight changes could be measured. Figures 24 through 26 show the effects of compressional forces of 2,000, 3,000 and 5,000 lbs., while Figures 27 and 28 are composites comparing the effects of the various pressures for the 105°C and 165°C peaks, respectively.

The effect of increasing pressure was to increase the rate at which water was transferred, from being totally bound in the form which peaked at 105°C to being partially bound at both the 105°C and 165°C positions. In other words, as the pressure on the 1:1:2 mixture was increased, the size of the 105°C peak decreased in area while that of the 165°C peak increased in area at a faster rate. The areas are proportional to the enthalpies required to remove the water from the 105°C and 165°C positions. The greater
Figure 23. TGA data showing the weight changes that occur with time, for the 105°C and 165°C water peaks of the 1:1:2 PABA, oxalic acid and water mixture, when compressed at 1000 lbs. for 10 mins.
Figure 24. TGA data showing the weight changes that occur with time, for the 105°C and 165°C water peaks of the 1:1:2 PABA, oxalic acid and water mixture, when compressed at 2000 lbs. for 10 mins.
Figure 25. TGA data showing the weight changes that occur with time, for the 105°C and 165°C water peaks of the 1:1:2 PABA, oxalic acid and water mixture, when compressed at 3000 lbs. for 10 mins.
Figure 26. TGA data showing the weight changes that occur with time, for the 105°C and 165°C water peaks of the 1:1:2 PABA, oxalic acid and water mixture, when compressed at 5000 lbs. for 10 mins.
Figure 27. Comparison of the TGA data for the effect of different pressures on the 105°C water peak of the 1:1:2 PABA, oxalic acid and water mixture.
Figure 28. Comparison of the TGA data for the effect of different pressures on the 165°C water peak of the 1:1:2 PABA, oxalic acid and water mixture.
the value of the enthalpy, the greater the amount of water
removed, as would be expected. Plots of the enthalpy
(expressed as mcal/mg) versus time (in hours) are shown
in Figures 29 through 32 for pressures of 1,000, 2,000,
3,000 and 5,000 lbs. As with TGA, the data for the
1,000 lb. compression showed no discernible enthalpy
changes until 48 hours after compression. Figures 33 and
34 are composites comparing the effects of the various
pressures for the 105°C and 165°C peaks.

It was noticed that in all cases the curves appeared
to plateau and approach an apparent equilibrium. The
logarithms of the differences between the apparent
equilibrium value minus the values at 1 to 7 hours for the
165°C peak, and the logarithm of the zero to 7 hours minus
the apparent equilibrium value for the 105°C peak, were
plotted against time. The resultant curves are shown in
Figures 35 through 38. The curves indicate apparent first-
order kinetics and the slopes of the lines (Table VII) give
the apparent first-order exponential rate constants.

Figures 39 and 40 show the TGA results for the 1:1:2
mixture compressed at 20,000 lbs. It was noted that the
rate constants lay between those of the 2,000 and 3,000 lbs.
compressed samples. It would seem that the rate constant
goes through a maximum then falls off as the pressure is
increased further. The cause of this phenomenon is not
Figure 33. Comparison of the DSC data for the effect of different pressures on the 105°C water peak of the 1:1:2 PABA, oxalic acid and water mixture.
Figure 34. Comparison of the DSC data for the effect of different pressures on the 165°C water peak of the 1:1:2 PABA, oxalic acid and water mixture.
Figure 37. Semilogarithmic plots of the difference between the enthalpy at time $t$, $\Delta H$, and the equilibrium value $\Delta H_e$, versus time, for the 105°C water peak of the 1:1:2 mixture, when subjected to various pressures.
Figure 38. Semilogarithmic plots of the difference between the enthalpy at equilibrium $\Delta H_e$, and the value at time $t$, $\Delta H$, versus time, for the 1650°C water peak of the 1:1:2 mixture, when subjected to various pressures.
\[
\begin{align*}
\text{TIME (HRS)} & \quad \text{% \, w/w \, WATER} \\
(X_e - X) & \quad (X_e - X)
\end{align*}
\]

- 105°C
- 165°C
TABLE VII

Effect of Pressure, at Constant Time of Compression, on the Rate Constants for Complex Formation

<table>
<thead>
<tr>
<th>Pressure (lbs.)</th>
<th>Rate constant $k$ hours$^{-1}$</th>
<th>TGA</th>
<th>DSC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>105°C peak</td>
<td>165°C peak</td>
<td>105°C peak</td>
</tr>
<tr>
<td>1,000</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>2,000</td>
<td>0.122</td>
<td>0.122</td>
<td>0.102</td>
</tr>
<tr>
<td>3,000</td>
<td>0.260</td>
<td>0.200</td>
<td>0.180</td>
</tr>
<tr>
<td>5,000</td>
<td>0.405</td>
<td>0.400</td>
<td>0.320</td>
</tr>
<tr>
<td>20,000</td>
<td>0.177</td>
<td>---</td>
<td>0.167</td>
</tr>
</tbody>
</table>

immediately apparent and investigation of this is suggested for a later study.

D. The Kinetic Effect of Various Times of Compression, at Constant Pressure, on the 1:1:2 PABA:Oxalic Acid:Water Mixture

Figures 41 through 45 show the effects of various times of compression at constant pressure, on the weight of water associated with the 105°C and 165°C endothermic peaks, from TGA data. Figures 46 and 47 are composites comparing the effects of the various compressional times. In the case (Figure 41, zero time sample) where the pressure was brought up to 5,000 lbs. and then released immediately, no
Figure 41. TGA data showing the effect of compressing the 1:1:2 mixture to 5000 lbs., then immediately releasing the pressure.
Figure 42. TGA data showing the effect of compressing the 1:1:2 mixture at 5000 lbs. for 1 min.
Figure 43. TGA data showing the effect of compressing the 1:1:2 mixture at 5000 lbs. for 2 mins.
Figure 44. TGA data showing the effect of compressing the 1:1:2 mixture at 5000 lbs. for 5 mins.
Figure 45. TGA data showing the effect of compressing the 1:1:2 mixture at 5000 lbs. for 10 mins.
Figure 46. Comparison of the TGA data for the effect of different times of compression on the 105°C water peak of the 1:1:2 mixture.
Figure 47. Comparison of the TGA data for the effect of different times of compression on the 165°C water peak of the 1:1:2 mixture.
weight changes were evident until 24-48 hours after compression. Figures 48 through 52 show the changes in enthalpy associated with the removal of water at the 105°C and 165°C peaks with increased time of compression, and Figures 53 and 54 are composites comparing the effects of various compression times. Again, virtually no changes were evident, in the zero time of compression samples, until 24-48 hours after compression.

The effect of increasing the time of compression was to increase the rate at which the 105°C peak decreased in area and the 165°C peak increased in area. The enthalpies (Figures 48-54) and percentage w/w of water (Figures 41-47) were plotted versus time, and log plots of the differences of these values from the equilibrium values were also plotted versus time (Figures 55-58).

The exponential rate constants obtained from the slopes of these curves are summarized in Table VIII.

The results of this last study showed that with increased time of compression, the rate of formation of the 1:1:1 complex increased at constant pressure as evidenced by the increase in rate constants. Also, the rate constants for the removal of water from the 105°C position, and the rate of appearance of water at the 165°C, are very close. Figure 59 shows plots of the apparent first-order rate constants versus compressional force for the DSC and TGA data from Table VII. The resulting curves indicate a
Figure 53. Comparison of the DSC data for the effect of different times of compression on the 105°C water peak of the 1:1:2 mixture.
Figure 54. Comparison of the DSC data for the effect of different times of compression on the 165°C water peak of the 1:1:2 mixture.
Figure 57. Semilogarithmic plots of \( \Delta H - \Delta H_e \) versus time, for the 105°C water peak of the 1:1:2 mixture, for different times of compression.
Figure 58. Semilogarithmic plots of ($\Delta H_e - \Delta H$) versus time, for the 165°C water peak of the 1:1:2 mixture, for different times of compression.
Figure 59. Effect of pressure on the rate constant for the formation of the 1:1:1 complex from the 1:1:2 mixture.
### TABLE VIII

Effect of Time of Compression, at a Constant Pressure of 5,000 lbs., on the Rate Constants for Complex Formation

<table>
<thead>
<tr>
<th>Time of compression (min)</th>
<th>Rate constant k hours$^{-1}$</th>
<th>TGA</th>
<th>DSC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>105°C peak</td>
<td>165°C peak</td>
</tr>
<tr>
<td>0</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>1</td>
<td>0.099</td>
<td>0.102</td>
<td>0.109</td>
</tr>
<tr>
<td>2</td>
<td>0.174</td>
<td>0.188</td>
<td>0.183</td>
</tr>
<tr>
<td>5</td>
<td>0.191</td>
<td>0.200</td>
<td>0.230</td>
</tr>
<tr>
<td>10</td>
<td>0.405</td>
<td>0.400</td>
<td>0.320</td>
</tr>
</tbody>
</table>

A linear relationship between the rate constant and pressure. Figure 60 shows plots of the apparent first-order rate constants obtained from Table VIII versus the time of compression. The resulting curves indicate that the relationship between the time of compression and the rate constant is nonlinear.

It was interesting to note that the rate constants obtained by both TGA and DSC are of the same order of magnitude. This is to be expected since the same phenomenon is being measured.
Theory

The foregoing results indicated that the rate of transfer of water from the 105°C position to the 165°C position occurred by apparent first-order kinetics. If it is assumed that the rate of formation of the 1:1:1 complex is the same as the rate of transfer of water between peak positions, and also that the rate approaches an equilibrium value, then the type of kinetics that apply can be considered those of

\[ \begin{align*}
A & \xrightarrow{k_+} B \\
& \xleftarrow{k_-}
\end{align*} \]

where A refers to the aged mixture and B the complex.

Equation 4, page 21,

\[ -\frac{dA}{dt} = \frac{dB}{dt} = \frac{dX}{dt} = k_+(A_0 - X) - k_-X \]  \hspace{1cm} (Eq. 2)

on integration and taking into account the equilibrium condition, yields:

\[ \ln(X_e - X) = -kt + \ln X_e \]  \hspace{1cm} (Eq. 3)

or \[ \log(X_e - X) = -\frac{kt}{2.303} + \log X_e \]  \hspace{1cm} (Eq. 4)

For the TGA results for the appearance of the 165°C peak, and hence the complex, a plot of \( \log(X_e - X) \) versus \( t \) will yield a straight line with slope equal to \( -\frac{k}{2.303} \) and
intercept \( \log X_e \). Multiplying the slope by 2.303 yields the exponential rate constant. For the disappearance of the 105\(^{\circ}\) C peak where

\[
\log(X - X_e) = -\frac{kt}{2.303} + \log(X_0 - X_e) \quad (\text{Eq. 5})
\]

a plot of \( \log(X - X_e) \) versus \( t \) will yield a straight line with slope equal to \(-\frac{kt}{2.303}\). Multiplying the slope by 2.303 again yields the exponential rate constant. The same equation can be applied to the DSC data because \( X \) is proportional to \( \Delta H \) (enthalpy at any time \( t \)), and \( X_e \) is proportional to \( \Delta H_e \) (equilibrium enthalpy). Then

\[
\log(\Delta H_e - \Delta H) = -\frac{kt}{2.303} + \log \Delta H_e \quad (\text{Eq. 6})
\]

applies to the 165\(^{\circ}\)C peak and

\[
\log(\Delta H - \Delta H_e) = -\frac{kt}{2.303} + \log(\Delta H_0 - \Delta H_e)
\]

(\text{Eq. 7}) applies to the 105\(^{\circ}\)C peak. The exponential rate constants are calculated from the semilogarithmic plots as shown above. A comparison of the rate constants for the 165\(^{\circ}\)C pressure study (A), both DSC and TGA, and the same constants (B) calculated by the method of Carstensen, \textit{et al.} (72) are shown in Table IX.
TABLE IX
Comparison of the Rate Constants (k) Obtained in the 165°C Pressure Study and the Same Constants Calculated by the Method of Carstensen (72)

<table>
<thead>
<tr>
<th>Pressure (lbs.)</th>
<th>Rate constant (hrs⁻¹)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DSC</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>2,000</td>
<td>0.104 0.144</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3,000</td>
<td>0.150 0.170</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5,000</td>
<td>0.330 0.410</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TGA</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>0.122 0.130</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.200 0.196</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.400 0.370</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The agreement between the results obtained by both methods is fairly close. One disadvantage of the Carstensen method was that the values for the time intervals had to be chosen very carefully. If not, rate constants would result which were two or three times greater than would be expected from the method used in this study. This became evident in calculating the 2,000 lb. rate constants.
SUMMARY

The effect of pressure on solid state interactions has been investigated. Initially, solid complexes were prepared and their stoichiometries determined by various methods. After selection of the 1:1:1 p-aminobenzoic acid:oxalic acid:water complex as a model or reference, its nature and properties were determined. Then, various molecular mixtures were prepared containing different molar quantities of water and compressed at constant pressure and constant time. Compressions were carried out using a hydraulic laboratory press and a specially designed punch and die holder. It was shown that increased water content brought about increased interaction under pressure. This study indicated that the 1:1:2 PABA:oxalic acid:water mixture would be suitable for subsequent investigations. An aged sample of the 1:1:2 compressed mixture was compared with the 1:1:1 complex, by means of DSC thermograms, through a series of compressions and a rehydration. The results indicated that the 1:1:2 mixture had been converted to the 1:1:1 complex under pressure. Water was "squeezed" from the mixture on its initial compression.

To show the effect of various pressures on the kinetics of complex formation, the 1:1:2 mixture was compressed at different pressures for a constant time. Increased pressure brought about an increase in the rate of complex formation, and the interaction proceeded by apparent first-order
kinetics. The rate constants were determined for both the DSC and TGA methods of analysis. The effect of time on compression at a constant pressure was investigated using the 1:1:2 mixture. Increased time of compression brought about an increase in the rate of complex formation and hence the rate constants. This interaction also followed apparent first-order kinetics. A linear relationship was found to exist between the rate constants and the compressional force, whereas a nonlinear relationship existed between the rate constants and the time of compression.

The study of the complex containing 1 mole \( \text{p-aminobenzoic acid:1 mole caffeine} \) showed that it also contained 3 moles of water and was not anhydrous as previously reported. Another study on the interaction in solution of succinamic acid with PABA and MABA showed that these were not physical interactions, as a new chemical bond was formed in each case with the elimination of ammonia.

All quantitative work was carried out using TGA and DSC, although some qualitative information was obtained from nmr, ir, and X-ray studies. This application of DSC and TGA to the investigation of the kinetics of complex formation under pressure is a new one and should find widespread application in the future as more solid state interactions are investigated.
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APPENDICES
APPENDIX A

NUCLEAR MAGNETIC RESONANCE SPECTRA
KEY TO APPENDIX A

I  1:1:1 PABA:oxalic acid:water complex
IV 1:1 PABA:oxalic acid complex (1:1:1 dried P₂O₅, 60°C, 22 days)
V  2:1 PABA:oxalic acid complex
VIII  2:1 MABA:oxalic acid complex
IX  N-(3-Carboxyphenyl)-succinamic acid
X  N-(4-Carboxyphenyl)-succinamic acid
XI  Aldrich Chemical cat. #S38150-0
DATE: 8/11/99

SAMPLE: PABA: 0.04%/C 80%/H_2O (1:1:1)

COMPLEX

RING H

ALPHA H

COOH

NH

COOH

COOH

H_2O

Solvent

Temperature

Filter Bandwidth

RF Field

Sweep Time

Sweep Width

Sweep Offset

Spectrum Amp.

Integral Amp.

SMARKS

PPM (T)

6.0

7.0

8.0

9.0

10

0

He

PPM (δ)

4.0

3.0

2.0

1.0

0

148
APPENDIX B

INFRARED SPECTRA
<table>
<thead>
<tr>
<th>Key</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1:1:1 PABA:oxalic acid:water complex</td>
</tr>
<tr>
<td>II</td>
<td>1:1:1 PABA:oxalic acid:water complex compressed</td>
</tr>
<tr>
<td>IV</td>
<td>1:1 PABA:oxalic acid complex (1:1:1 dried $P_2O_5$, 60°C, 22 days)</td>
</tr>
<tr>
<td>V</td>
<td>2:1 PABA:oxalic acid complex</td>
</tr>
<tr>
<td>VII</td>
<td>Nujol</td>
</tr>
<tr>
<td>IX</td>
<td>N-(3-Carboxyphenyl)-succinamic acid</td>
</tr>
<tr>
<td>X</td>
<td>N-(4-Carboxyphenyl)-succinamic acid</td>
</tr>
<tr>
<td>XI</td>
<td>Aldrich Chemical cat. #S38150-0</td>
</tr>
</tbody>
</table>